DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

d13786

CBER-98-024

Warning Letter

August 14, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Richard Ellis
Allergy Laboratories, Inc.
P.O. Box 26492
Oklahoma City, OK 73126-1492

Dear Mr. Ellis:

The Food and Drug Administration (FDA) conducted an inspection of Allergy Laboratories, Inc., P.O. Box 26492, Oklahoma City, OK, between May 18-22, 1998. During the inspection, FDA investigators identified violations of Section 501 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), Section 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR), Subchapter C, Part 211 and Subchapter F, Parts 600-680. These documented violations include, but are not limited to, the following:

1. Failure to establish and follow appropriate written procedures, designed to prevent microbial contamination of drug products purporting to be sterile [21 CFR 211.113(b)], in that:

   a. the media fill procedure entitled " [redacted] " does not provide for the simulation of actual production activities and/or worst case production conditions. Additionally, the procedure does not provide for testing of the bulk extract which is stored for [redacted] subsequent to the [redacted] process.

   b. endotoxin and microbial analysis of the WFI is not performed daily or on a schedule which is consistent with manufacturing operations.

2. Failure to establish written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or represented to possess [21 CFR 211.100(a)], in that:

a. there are no procedures established addressing:

i. the manufacturing process utilized in repackaging finished drug products from a — container into ——— containers;

ii. product recalls;

iii. adverse events reporting;

iv. change control of processes and/or specifications; and

v. changeover of products in multi-product production areas.

b. the standard operating procedure (SOP) entitled " ——————————— ——————" does not address performing corrective action in the event of a bulk or finished product sterility failure.

c. total particle counts are not determined on a daily basis or during periods of manufacturing in the class — areas as prescribed in the SOP entitled " ——— ——— ".

3. Failure to ensure that equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and adequate size to facilitate operations for its intended use [21 CFR 211.63], in that the Water for Injection (WFI) system is inadequately designed. For example:

a. sections of copper piping and flexible silicon tubing are not sloped in a fashion to facilitate adequate draining.

b. piping and equipment couplings used in the WFI system have threaded unions.

4. Failure to routinely calibrate, inspect, or check for accuracy and to exercise appropriate controls for automatic, mechanical, or electronic equipment or other types of equipment, including computers, used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed so as to assure performance [21 CFR 211.68], in that:

a. thermometers which are used to monitor the temperature of the WFI system are not calibrated.

b. thermocouples which were used in the heat distribution study of the autoclave were not calibrated.

c. the — Computer database and computer program used for inventory tracking and distribution of final product has not been validated.

d. Installation Qualification (IQ), Operation Qualification (OQ), and worst case operating conditions were not performed as part of the validation study for the incubator.

5. Failure to clean, maintain, and sanitize equipment, utensils, and supplies at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product, to establish or maintain written procedures for cleaning and maintenance of equipment, and to maintain records [21 CFR 211.67 and 600.12], in that:

a. equipment has not been maintained or replaced as per the SOP entitled " ". For example:

i. point of use filters for the have not been replaced.

ii. the pre-filters and filters for the air handling units, which supply air to classified areas, have not been replaced every months.

iii. the laminar flow hood pre-filters have not been replaced

b. there is no documentation indicating that daily WFI system inspection checks were performed on the following production dates, , and

c. the filters were labeled as being serviced on 4/13/98 and 4/14/98 however, there was no documentation that service was performed on these dates in the WFI maintenance log book.

d. the cleaning procedures utilized in cleaning the shared product contact parts of equipment, which is used in the aseptic filling of final product, have not been validated.

6. Failure to demonstrate that the sterility of each lot of each product by the correct performance of tests [21 CFR 610.12(a)(1) and 610.12(b)(3)], in that:

a. the microbial growth medium used in the sterility testing of allergenic extract diluent solutions is not incubated for the required 14 day period.

b. the sterility retest procedure in the SOP entitled " " stated that . However, the acceptable procedure for performing a second retest requires that the number of specimens tested should be doubled the number tested in the first stage,

7. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, test procedures designed to assure that

components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)], in that:

a. growth promotion qualification of the media used for environmental monitoring (Rodac plates) has not been performed.

b. testing is not performed to verify the survival time and kill time qualities of the biological indicators (BI).

8. Failure to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. For example:

a. ———— finished product and bulk sterility test failure reports did not indicate any corrective action as being performed.

b. there is no evaluation or follow up investigation performed to determine the effectiveness of the corrective action resulting from a sterility test failure.

9. Failure to ensure that laboratory records include complete data derived from all tests necessary to assure compliance with established specifications and standards [21 CFR 211.194], in that:

a. growth promotion test results for growth medium prepared in-house are not reviewed and approved by supervisory personnel.

b. the total particulate count reports for class — areas are not reviewed and approved by supervisory personnel. Additionally, the individual who performed the particulate counts is not identified on the reports.

10. Failure to handle and store components and drug product containers and closures in a manner to prevent contamination [21 CFR 211.80(b)], in that:

a. lawn equipment and petroleum products are stored adjacent to shipping materials.

b. sterile empty vials, which were approved for release and distribution, are stored adjacent to chemicals used for cleaning.

11. Failure to ensure that the ventilation system is arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product, in that unidirectional airflow in the class — aseptic filling suite has not been established [21 CFR 600.11(a)].

12. Failure to establish written procedures so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures, in that

there are no procedures for the evaluation and annual review of the manufacturing operations [21 CFR 211.180(e)].

13. Failure to inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application(s), in that CBER was not notified of the installation of a ——— in February 1997 [21 CFR 601.12(a)].

Additionally, FDA investigators disclosed during the most recent inspection of your firm that you are presently engaged in the practice of repackaging finished drug products from — containers, which were released and approved for distribution, to — containers of final product. Please be advised that each change in the product, production processes, quality controls, equipment, facilities, responsible personnel, or labeling operations may require that you notify FDA of the change and/or require that you submit a supplement(s) to your license as outlined in 21 CFR 601.12. You have not demonstrated or established, prior to distribution, that the repackaging of final product from — containers to — containers has not adversely effected the identity, strength, quality, purity or potency of the product as the change may relate to the safety or effectiveness of the product.

Neither this letter nor the list of inspectional observations (Form FDA-483) which was issued to you at the conclusion of the inspection are meant to be an all-inclusive list of violations occurring at your facility. We remind you that it is your responsibility as a manufacturer of licensed allergenic products to ensure that your operations are in full compliance with all applicable federal laws and regulations.

You should take prompt action to correct these violations, and those noted during previous inspections. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction, or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We acknowledge receipt of your letter dated May 21, 1998 in response to the May 13, 1998 letter issued by the FDA to all licensed Allergenic Product manufacturers who obtain source material from ——— In your letter, you inquired whether source material obtained from — prior to the issuance of the May 13, 1998 letter, may be used in your U.S. licensed products. Please note that it is your responsibility, under current applicable regulations, to ensure that all source material, whether obtained before or after the issuance of the May 13, 1998 letter, has been collected and processed in accordance with applicable regulations and that you have established procedures to appropriately determine the acceptability of such source materials for use in the manufacture of licensed products.

Additionally, we acknowledge receipt of your June 8, 1998, response to the Form FDA-483, which was issued at the conclusion of the most recent inspection of your establishment. However, we have not yet completed our review of your response and our comments to your letter will be addressed under separate cover.

Please notify this office in writing of the additional steps you have taken or will take to correct or prevent the listed violations from recurring. Your response should be sent to me at the following address: Food and Drug Administration; Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448. You may reference your June 8, 1998, letter in responding to this Warning Letter.

If you have any questions or comments regarding this letter, please contact me at 301-827-6190.

Sincerely,

Anita Richardson

for Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics
Evaluation and Research